PATENT COOPERATION TREATY

M176

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/050001	06.01.2005	08.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07D405/04, A61K31/506, A61P33/06, C07F7/08

Applicant
MEDIVIR AB

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/050001

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/050001

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1,2,12,13 (partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1,2,12,13 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/050001

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,7,18
	No:	Claims	1,2,4-6,8-17,19-24
Inventive step (IS)	Yes:	Claims	3,7,18
	No:	Claims	1,2,4-6,8-17,19-24
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2005/050001

Re Item III.

Present claims 1,2,12,13 relate to a rather elevated number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds wherein A is O or CH2, B is CHR3, R1=H, R3 is H, F, OH, NH2 or a pharmaceutically acceptable ester, amide of ether thereof, D is O or NR5.
Remark: the structures drawn up for examples 21,27,28,29 do not correspond to the names given accordingly in the description.

Re Item V.

1 Reference is made to the following document:

D1 : HIDALGO-ZARCO, FERNANDO ET AL: "Kinetic properties and inhibition of the dimeric dUTPase-dUDPase from Leishmania major" PROTEIN SCIENCE , 10(7), 1426-1433 CODEN: PRCIEI; ISSN: 0961-8368, 2001, XP008047778

D2: CANO, V. ET AL: "Monometoxytrityl derivatives of uridine as inhibitors of a human recombinant UDP-glucuronosyltransferase: UGT16" LIFE SCIENCES , 61(1), PL1-PL8 CODEN: LIFSAK; ISSN: 0024-3205, 1997, XP008047794

D3: US-A-5 559 101 (WEIS ET AL) 24 September 1996 (1996-09-24)

D4: O'DELL, C. ALLEN ET AL: "Carbocyclic analogs of 3',4'-didehydro-2'-deoxyribofuranosyl-2,4(1H,3H)- pyrimidinediones" NUCLEOSIDES & NUCLEOTIDES , 13(9), 1929-37 CODEN: NUNUD5; ISSN: 0732-8311, 1994, XP008047788

D5: NIIHATA, SHIGEO ET AL: "Synthesis of 2',3'-didehydro-2',3'-dideoxy nucleosides from 2',2'-bis(phenylthio) nucleoside analogs" BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN , 68(8), 2327-9 CODEN: BCSJA8; ISSN: 0009-2673, 1995, XP008047808

D6: TAKAMATSU, SATOSHI ET AL: "Convenient synthesis of fluorinated

nucleosides with perfluoroalkanesulfonyl fluorides" NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS , 21(11 & 12), 849-861 CODEN: NNNAFY; ISSN: 1525-7770, 2002, XP008047806

D7: HORWITZ, JEROME P. ET AL: "Nucleosides. IX. The formation of 2',3'-unsaturated pyrimidine nucleosides via a novel .beta.-elimination reaction" JOURNAL OF ORGANIC CHEMISTRY , 31(1), 205-11 CODEN: JOCEAH; ISSN: 0022-3263, 1966, XP008047787

D8: VAN AERSCHOT A. ET AL.: "2,3'- DIFLUORO- AND 3'-AZIDO-2'-FLUORO SUBSTITUTED DIDEOXYPYRIMIDINES AS POTENTIAL ANTI-HIV AGENTS" BULL. SOC. CHIM. BELG, vol. 98, no. 12, 1989, pages 937-941, XP008047840

D9: US-A-5 410 033 (CLIVE ET AL) 25 April 1995 (1995-04-25)

D10: PATENT ABSTRACTS OF JAPAN vol. 016, no. 289 (C-0956), 26 June 1992 (1992-06-26) & JP 04 077485 A (YAMASA SHOYU CO LTD), 11 March 1992 (1992-03-11)

D11: WO 95/07287 A (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE (CNRS; GOSSELIN, GILLES;) 16 March 1995 (1995-03-16)

D12: BEACH J W ET AL: "A highly stereoselective synthesis of anti-HIV 2',3'-dideoxy-" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 57, no. 14, 1992, pages 3887-3894, XP002953555 ISSN: 0022-3263

D13: WO 97/37691 A (LYNX THERAPEUTICS, INC) 16 October 1997 (1997-10-16)

D14: VON JANTA-LIPINSKI M ET AL: "Newly synthesized L-enantiomers of 3'-fluoro-modified beta-2'-deoxyribonucleoside 5'-triphosphates inhibit hepatitis B DNA polymerases but not the five cellular DNA polymerases alpha, beta, gamma, delta, and epsilon nor HIV-1 reverse transcriptase." JOURNAL OF MEDICINAL CHEMISTRY. 4 JUN 1998, vol. 41, no. 12, 4 June 1998 (1998-06-04), pages 2040-2046, XP002330488 ISSN: 0022-2623

D15: PATENT ABSTRACTS OF JAPAN vol. 018, no. 004 (C-1149), 6 January 1994 (1994-01-06) & JP 05 247082 A (JAPAN TOBACCO INC), 24 September 1993 (1993-09-24)

D16: PATENT ABSTRACTS OF JAPAN vol. 016, no. 249 (C-0948), 8 June

1992 (1992-06-08) & JP 04 054193 A (JAPAN TOBACCO INC; others: 01), 21 February 1992 (1992-02-21)

2 CLAIMS 1,2,4-6,8-17,19-24

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1,2,4-6,8-13,15-17,19-24 is not new in the sense of Article 33(2) PCT.
Document D1 discloses (see the passages cited in the search report) that the activity of Leishmania dUTPase is efficiently inhibited by the nucleoside 5'-O-(4-4'-dimethoxytrityl)-2'deoxyuridine. The existence of specific inhibition and the apparent structural and kinetic differences (reflected in different binding strength of dNTPs) with other eukaryotic dUTPases suggest that the present enzyme might be exploited as a target for new drugs against leishmaniasis.

2.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 12,13,15-17,19-22 is not new in the sense of Article 33(2) PCT.
Document D2 discloses (see the passages cited in the search report) 5'-trityl uridine and 5'-(4-monomethoxy)-trityl uridine and their use as inhibitors of human recombinant UGT1*6.

2.3 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 12,13,15-17,19-21 is not new in the sense of Article 33(2) PCT.
Document D3 discloses (see the passages cited in the search report) the compounds 2'-deoxy-5'-O-(4-monomethoxytrityl)-.beta.-L-uridine and 2',3'-dideoxy-5'-O-(4-monomethoxytrityl)-.beta.-L-uridine (Cf example 20 of present application).

2.4 The present application does not meet the criteria of Article 33(1) PCT, because the

subject-matter of claim 12-17,19-21 is not new in the sense of Article 33(2) PCT.
Document D4 discloses (see the passages cited in the search report) the compounds 1-[3-hydroxy-4-[(triphenylmethyl)oxymethyl]cyclopentyl-2,4(1H,3H)- pyrimidinedione and 1-[4-[(triphenylmethyl)oxymethyl] cyclopent-2-en-yl- 2,4(1H,3H)- pyrimidinedione

2.5 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 12-14,16-20 is not new in the sense of Article 33(2) PCT.
Document D5 discloses (see the passages cited in the search report) the compound 1-[5(O-t-Butyldiphenylsilyl)-2,3-dideoxy-beta-D-glycero-pent-2-enofuranosyl]uracil

2.6 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 12-17,19-21 is not new in the sense of Article 33(2) PCT.
Document D6 discloses (see the passages cited in the search report) the compounds 2',3'-Dideoxy-3'-fluoro-5'-O-(triphenylmethyl)-uridine,
1-[2-deoxy-5-O-(triphenylmethyl)-beta-D-xylofuranosyl]uracil, and
2',3'-dideoxy-5'-O-(triphenylmethyl)-uridin-2'-ene.

2.7 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 12-17,19-21 is not new in the sense of Article 33(2) PCT.
Document D7 discloses (see the passages cited in the search report) the compound 2',3'-dideoxy-5'-O-(triphenylmethyl)-uridin-2'-ene.

2.8 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 12,13,15-17,19-22 is not new in the sense of Article 33(2) PCT.
Document D8 discloses (see the passages cited in the search report) the compounds 2'-fluoro-5'-O-trityluridine and 2,3'-difluoro-5'-O-trityluridine.

2.9 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 12,13,15-17,19-21 is not new in the sense of Article 33(2) PCT.
Document D9 discloses (see the passages cited in the search report) the preparation of 2', 3'-Didehydro-2',3'-dideoxy-5'-0-(triphenylmethyl)uridine

2.10 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.
Document D10 discloses (see the passages cited in the search report) the compound 1-[5-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-2,5-dihydro-2-furanyl]-2,4(1H,3H)-pyrimidinedione.

2.11 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 12,13,15-17,19,20 is not new in the sense of Article 33(2) PCT.
Document D11 discloses (see the passages cited in the search report) the compound 5'-O-tertiobutyldiphenylsilyl-2'.3'-dideoxy-beta-L-uridine

2.12 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 12-14,16,17,19,20 is not new in the sense of Article 33(2) PCT.
Document D12 discloses (see the passages cited in the search report) the compounds
1-[5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-beta-D-glycero-pentafuranosyl]uracil and
1-[5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-beta-D-glycero-pent-2-eno- furanosyl]uracil.

2.13 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 12,13,15-17,19-21 is not new in the sense of Article 33(2) PCT.
Document D13 discloses (see the passages cited in the search report) the compound 5 '-Dimethoxytrityl-O-2'-fluoro-3 '-aminouridine (5 '-DMT-O-2'-fluoro- 3'-aminouridine).

2.14 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 12,13,15-17,19-21 is not new in the sense of Article 33(2) PCT.
Document D14 discloses (see the passages cited in the search report) the compounds 2',3'-Dideoxy-3'-fluoro-5'-O-(triphenylmethyl)-uridine and
2'-deoxy-3'-fluoro-5'-O-(triphenylmethyl)-uridine

2.15 The present application does not meet the criteria of Article 33(1) PCT, because the

subject-matter of claim 12,13,15-17,19,20 is not new in the sense of Article 33(2) PCT.
Document D15 discloses (see the passages cited in the search report) the compound 5-O-(tert-butyldiphenylsilyl)-2,3-dideoxy-2-fluoro-D-erythro-uracil.

2.16 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 12-14,16,17,19,20 is not new in the sense of Article 33(2) PCT.
Document D16 discloses (see the passages cited in the search report) the compound 5-O-(tert-butyldiphenylsilyloxymethyl]-2,5-dihydro-2-furanyl-2,4(1H3H)-pyrimidinedione].

3 CLAIMS 1,2,4-6,8-17,19-24
Claims 1,2,4-6,8-17,19-24 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).